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ABBREVIATION
AED Antiepileptic drug

AIM To determine neurocognitive performance and behavioural problems in children with Panayiotopoulos syndrome.

METHOD All 18 children (10 females, 8 males; mean age 4y 7mo; SD 1y 10mo) diagnosed with Panayiotopoulos syndrome at the Kempenhaeghe Epilepsy Center in the Netherlands between 2010 and 2017 were analysed retrospectively. All underwent a neuropsychological/behavioural assessment, an academic assessment, and a 24-hour electroencephalogram.

RESULTS Mean full-scale IQ (93.5; range 76–123; p=0.04) and performance IQ (93.2; range 76–126; p=0.04) were within the normal range, although significantly lower compared to the normative mean. Verbal IQ (96.3; range 76–118) and processing speed (96.1; range 74–114) were not significantly lower. Simple auditory/visual reaction times, visual attention, visual-motor integration, and verbal memory were significantly lower compared to normative values. On average, patients with Panayiotopoulos syndrome were 8 months behind in arithmetic speed and 11 months behind in reading speed for the number of months in school. Behavioural questionnaires revealed significantly higher scores on reported internalizing behavioural problems.

INTERPRETATION Children with Panayiotopoulos syndrome demonstrated diffuse cognitive dysfunction in full-scale IQ, performance IQ, visual attention, visual-motor integration, and verbal memory. A high incidence of internalizing behavioural problems was reported. This strongly suggests neuropsychological and behavioural comorbidity in children with Panayiotopoulos syndrome.

In Panayiotopoulos syndrome, autonomic seizures occur in an otherwise typically developing child.[1–3] Incidence has been estimated at 0.8 per 100 000 children aged younger than 16 years.[4] Seizures are often long in duration, infrequent (in some, limited to one episode), and occur frequently during sleep.[1,5,6] Autonomic status epilepticus may present in up to 20% of children.[1,3,7,8] While Panayiotopoulos syndrome has been considered a type of occipital epilepsy, the interictal electroencephalogram (EEG) is characterized by multifocal (high-amplitude) spikes or sharp and slow waves, often, but not necessarily, in an occipital/posterior location.[1,6,9,10] In the majority of children with Panayiotopoulos syndrome, remission occurs 1 to 2 years after onset.[11]

Panayiotopoulos syndrome has been considered a benign epilepsy syndrome due to a good clinical prognosis; nevertheless, a few studies have observed (mild) neurocognitive deficits, such as lower performance in (subtests) of intelligence, visual-perceptual functioning, attention, semantic processing, arithmetic, language, and memory.[12–19]

Neurocognitive findings have raised subsequent hypotheses as to which brain areas may be involved in Panayiotopoulos syndrome. In particular, deficits in visual functioning have been postulated due to the frequent occipital location of epileptic activity. Nevertheless, results have been conflicting so far. De Rose et al.[15] reported visual-perceptual abnormalities in 7 out of 28 children with Panayiotopoulos syndrome and Lopes et al.[14] found lower mean performance in the copy task of the Rey–Osterrieth Complex Figure test in a case-control study (n=19). Furthermore, Lopes et al.[14] and Specchio et al.[6] (n=17) found low average scores in the

subtests of the Wechsler Intelligence Scale for Children, Third Edition, partly dependent on visual function. Lopes et al.[14] subsequently proposed a dysfunction in the parietal lobe due to impairments in visual-perceptual functioning and semantic processing. Hodges et al.[12] showed similar results for visual-perceptual dysfunction in a case series of three children, whereas Bedoin et al.[16] suggested frontal lobe disturbance based on a reduction in the ability to diffuse inhibition outside the attentional focus, which might be explained by the posterior-to-frontal propagation of interictal activity. Hence, current evidence is inconclusive, although cognitive functions or networks associated with the location of epileptiform activity in Panayiotopoulos syndrome are potentially at risk.

Additional information on neuropsychological functioning in Panayiotopoulos syndrome will contribute to the understanding of the impact of this allegedly benign epilepsy syndrome on neurocognition. Furthermore, since reports on potential behavioural problems are lacking, we were interested in the occurrence of behavioural problems in children with Panayiotopoulos syndrome. The aim of the current study was to report on neurocognitive functioning and behaviour in children diagnosed with Panayiotopoulos syndrome.

METHOD

Inclusion criteria

Patient files of children referred between 2010 and 2017 to the Kempenhaeghe Epilepsy Center, a tertiary epilepsy centre in the Netherlands, were searched for potential cases of Panayiotopoulos syndrome and re-evaluated based on clinical information and EEG records. Patients were included based on the following criteria: (1) seizures coinciding with autonomic symptoms; and (2) an EEG with (multi) focal spikes or sharp and slow waves, not necessarily in the occipital regions, compatible with Panayiotopoulos syndrome according to the International League Against Epilepsy guidelines.[20–22]

All children had a multidisciplinary assessment as part of routine interdisciplinary care, which included a medical assessment by a neurologist specialized in paediatric epilepsy, a 24-hour EEG, a neuropsychological/behavioural assessment by a trained neuropsychologist, and an academic assessment by a school expert.

The medical charts of all children with Panayiotopoulos syndrome were carefully inspected and clinical data such as age at onset, semiology, drug history, 24-hour EEG findings, and school performance were collected in an online data management system (Castor Electronic Data Capture, CIWIT B.V., Amsterdam, the Netherlands). All participating children and/or parents gave permission for the use of medical charts for research purposes. All included children and/or parents signed informed consent for use of medical charts for research purposes. This research protocol was approved by the local medical ethics committee in Kempenhaeghe.

What this paper adds

- Children with Panayiotopoulos syndrome are at risk for cognitive deficits in various cognitive domains.
- Children with Panayiotopoulos syndrome are also prone to internalizing behavioural problems.
- Mild-to-severe academic underachievement was present in more than half of the children with Panayiotopoulos syndrome.

Neuropsychological, achievement, and behavioural assessment

A description of the neuropsychological, achievement, and behavioural tests used is presented in Table S1 (online supporting information) and references to the test manuals are found in Appendix S1 (online supporting information).

Neuropsychological test results were assessed using Baron's distinction of different neurocognitive domains in child neuropsychology.[23] The following neurocognitive domains were assessed: intelligence; attention; visual-perceptual function; and learning/memory. In addition, achievement tests and proxy parental/teacher questionnaires on behaviour were used. Based on the assessments of a trained psychologist and academic evaluations by a trained school specialist, the presence of academic underachievement was scored as normal, mild-to-moderate, or severe. For this, we used the definition described by Massa et al. (Table S2, online supporting information).[24]

Statistical analysis

Raw scores of neuropsychological tests were converted into age-corrected standardized scores and transformed into z-scores (mean 0; SD 1) or a T score (mean 50; SD 10) based on normative data from the corresponding neuropsychological test manuals. A one-sample *t*-test was used to test whether the sample mean was different to the normative mean (i.e. a z-score of 0 or a T score of 50). The Wilcoxon signed-rank test was used to test whether the sample median was statistically different from the normative median (available from the corresponding neuropsychological test manuals) in those tests reporting in decile scores. All analyses were done with IBM SPSS Statistics 23 (SPSS Inc, Chicago, IL, USA). A p-value ≤ 0.05 indicated statistical significance.

RESULTS

Population

In total 18 children (10 females, 8 males; mean age 4y 7mo; SD 1y 10mo) met our inclusion criteria for Panayiotopoulos syndrome. The patient characteristics are presented in Table S2. All children were born after an uneventful pregnancy and did not have a history of abnormal cognitive or motor development before the onset of epilepsy. Two patients had a first-degree relative with epilepsy and two had a first-degree relative with a learning disorder. The median clinical follow-up time was 4 years 11 months (1y 5mo–11y). The most common clinical features during seizures are listed in Figure 1. Nine children experienced nocturnal seizures and three children had early

morning seizures. Median seizure duration was 45 minutes (range, approximately 1min–6.5h). Two children presented with status epilepticus at seizure onset. Total seizure frequency was low. Furthermore, the location of interictal epileptiform discharges on the EEG also varied widely between patients; in 13 out of 18, focal migration was observed during follow-up. Focal migration between EEGs has been described in the literature and is a common observation in Panayiotopoulos syndrome.[1,3]

The average time from seizure onset till seizure freedom was 2 years 6 months (SD 2y 2mo), defined as no seizures for at least 1-year. At the time of data collection, initial monotherapy failed in six patients and they had to be switched into another monotherapy. Two children received two antiepileptic drugs (AEDs) simultaneously. In four children, AED treatment was not initiated, and seven children were still using AEDs. Sixteen patients were seizure-free. In nine children, the last EEG was free of epileptiform discharges.

Neurocognitive performance

Results on neurocognitive performance are presented in Table 1 and Figure 2 (subtests of the Wechsler Intelligence Scale for Children and neurocognitive tests performed in a small subset of patients are available in Appendix S2, online supporting information). The average time from onset to neuropsychological testing was 2 years 10 months (SD 2y 6mo). Mean intelligence scores were within the average clinical range, although on the lower end of the average range: full-scale IQ (93.5; 76–123); performance IQ (93.2; 76–126); verbal IQ (96.3; 72–118); and processing speed (96.1; 74–113). Furthermore, full-scale IQ (p=0.04) and performance IQ (p=0.04) were significantly lower than the normative mean. Since intelligence was assessed with the Wechsler Preschool and Primary Scale of Intelligence, Third Edition in three children, analyses were also performed without these children, which yielded similar results.

Mean attention scores were significantly lower using the Bourdon-Vos speed of visual processing test (p<0.001) and in the Test of Everyday Attention for Children (Sky Search) for visual selective attention (p=0.006) compared to the normative mean. Sustained auditory attention measured with the Test of Everyday Attention for Children Score subtest; it did not differ significantly from the normative mean. The attention scores remained significantly lower after excluding two patients with attention-deficit/hyperactivity disorder from the analysis. Simple reaction times were significantly lower compared to the normative median for auditory (p=0.007 for the right side and p=0.01 for the left side) and visual stimuli (p=0.002 for the right side and p=0.001 for the left side). Visual reaction time had a median decile score of 1 for both hands. The binary choice reaction time (focused attention) and the computerized visual searching task did not differ significantly from the normative median.

The Beery–Buktenica tests showed significantly lower scores (p=0.006) on visual-motor integration compared to the normative mean. The results of the Beery–Buktenica test remained significant after excluding two patients with developmental coordination disorder from the analysis. The Rey Auditory Verbal Learning Test revealed significantly lower scores on the immediate (p=0.007) and delayed recall tasks (p=0.03). Age at onset or AED use did not correlate with neuropsychological test results. Neurocognitive results did not change when children who were not seizure-free were excluded.

Educational achievement

Mild-to-severe academic underachievement was observed in 10 patients (Table S2). Severe academic underachievement occurred in children with seizure onset at an early age. Children with Panayiotopoulos syndrome were on average 8 months behind in arithmetic speed based on the level they should be at in school (p=0.03) (Table 2). Furthermore, regarding reading speed, children with Panayiotopoulos syndrome were on average 11 months behind (p=0.004 for words and p=0.01 for sentences). Results in

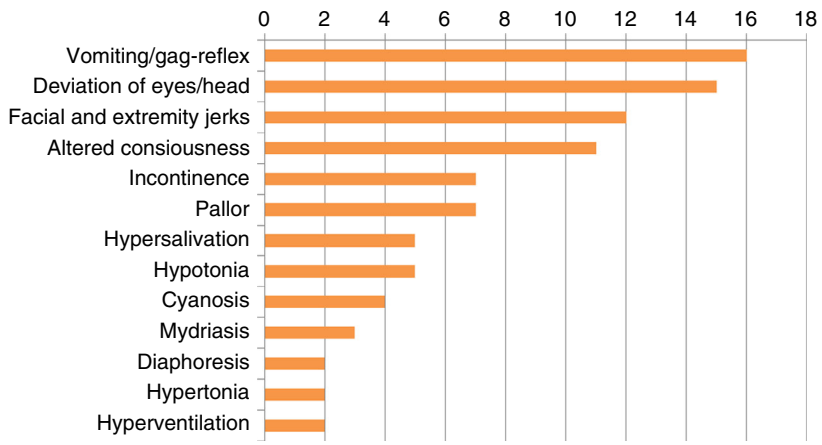

Figure 1: Frequency of patients with the most common semiological features in our study population (n=18). [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1: Neurocognitive performance in the study cohort

Cognitive domain	Test	Subscore	*n*	Mean z-score (95% CI) or median decile score [range]	*p*
Intelligence	WPPSI-III/WISC-III	Full-scale IQ	18	−0.43 (−0.85 to −0.02)	**0.04**
		Verbal IQ		−0.25 (−0.65 to 0.13)	0.18
		Performance IQ		−0.45 (−0.88 to −0.03)	**0.04**
		Processing Speed Index		−0.26 (−0.65 to 0.13)	0.18
Attention	Bourdon-Vos speed of visual processing	Speed	12	−1.50 (−2.01 to −0.99)	**<0.001**
		Accuracy		−0.25 (−1.11 to 0.61)	0.54
	Test of Everyday Attention for Children	Sky Search (attention score)	14	−0.67 (−1.10 to −0.23)	**0.006**
		Score! (correct)		−0.22 (−0.72 to 0.29)	0.37
	FePsy 2.0	Auditory reaction time (right)	13	3.00 [1–8]	**0.007**
		Auditory reaction time (left)		2.00 [1–10]	**0.01**
		Visual reaction time (right)	14	1.00 [1–9]	**0.002**
		Visual reaction time (left)		1.00 [1–7]	**0.001**
		Binary choice reaction time	12	7.50 [3–9]	0.17
		Computerized visual searching task (time)	11	4.00 [1–10]	0.72
		Computerized visual searching task (faults)		3.00 [1–10]	0.14
Visual-perceptual function	Beery–Buktenica Developmental Test of Visual-Motor Integration	Visual-motor integration	18	−0.66 (−1.10 to −0.21)	**0.006**
Verbal memory and learning	Rey Auditory Verbal Learning Test	Immediate recall	16	2.50 [1–10]	**0.007**
		Delayed recall	15	1.00 [1–10]	**0.03**

The results from each test were compared with the normative mean or median. Bold type indicates statistical significance of $p \leq 0.05$. CI, confidence interval; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence, Third Edition; WISC-III, Wechsler Intelligence Scale for Children, Third Edition.

arithmetic and reading speed did not correlate significantly with results on the Processing Speed Index.

Behaviour

The Childhood Behavior Checklist completed by parents was available for 17 children; a Teacher Report Form was available for nine children. Mean total problems and internalizing problems T scores were significantly higher than the normative mean of 50 in the Childhood Behavior Checklist as reported by parents. Externalizing problems did not differ significantly (Table 3 and Figure 3). Teachers did not report significantly higher scores on the Childhood Behavior Checklist indices.

DISCUSSION

This study in children with Panayiotopoulos syndrome demonstrates that neurocognitive performance was significantly lower compared to the normative mean in several domains. Full-scale and performance IQ were still within the average range, although at the lower end of the average range. Furthermore, our study observed impairment in attention, visual-motor integration, and verbal memory. Mild-to-severe academic underachievement was noted in 10 out of the 18 participating children with Panayiotopoulos syndrome. Severe academic underachievement occurred in children with an early age at onset. This was also reflected by a 7 to 11-month delay in the speed of arithmetic and reading. Finally, reports using validated questionnaires on behaviour in children with Panayiotopoulos syndrome have been lacking. This study found a high incidence of clinically relevant internalizing behavioural problems, as reported by parents.

The finding that these impairments occur across several different neurocognitive domains, as also observed by others,[12,14–16] probably indicates that multiple brain areas and networks are involved in mediating the neurocognitive dysfunctions observed in children with Panayiotopoulos syndrome.

This may be related to the presence of multifocal epileptiform activity; however, this study did not aim to correlate the localization of epileptiform activity or epileptogenesis with cognitive measures. However, since epileptiform activity is often recorded in parietal-temporal-occipital regions in individuals with Panayiotopoulos syndrome, the parietal-temporal-occipital cortices or associated area may be involved in mediating the observed cognitive dysfunctions.[6] Our data suggest that visually demanding tasks are especially affected, for example, tasks involving visual selective attention, visual sustained attention, visual alertness, and visual-motor integration. This was also reflected in the visually demanding subtests of the Wechsler Intelligence Scale for Children, Third Edition, for example, object assembly (p=0.003), block design (p=0.08), and picture completion (p=0.08), although not all were significantly lower compared to the normative mean (Appendix S2). Interestingly, performance was normal on more complex visual tasks, which may require more activation of frontal areas,[25] such as binary choice reaction time, computerized

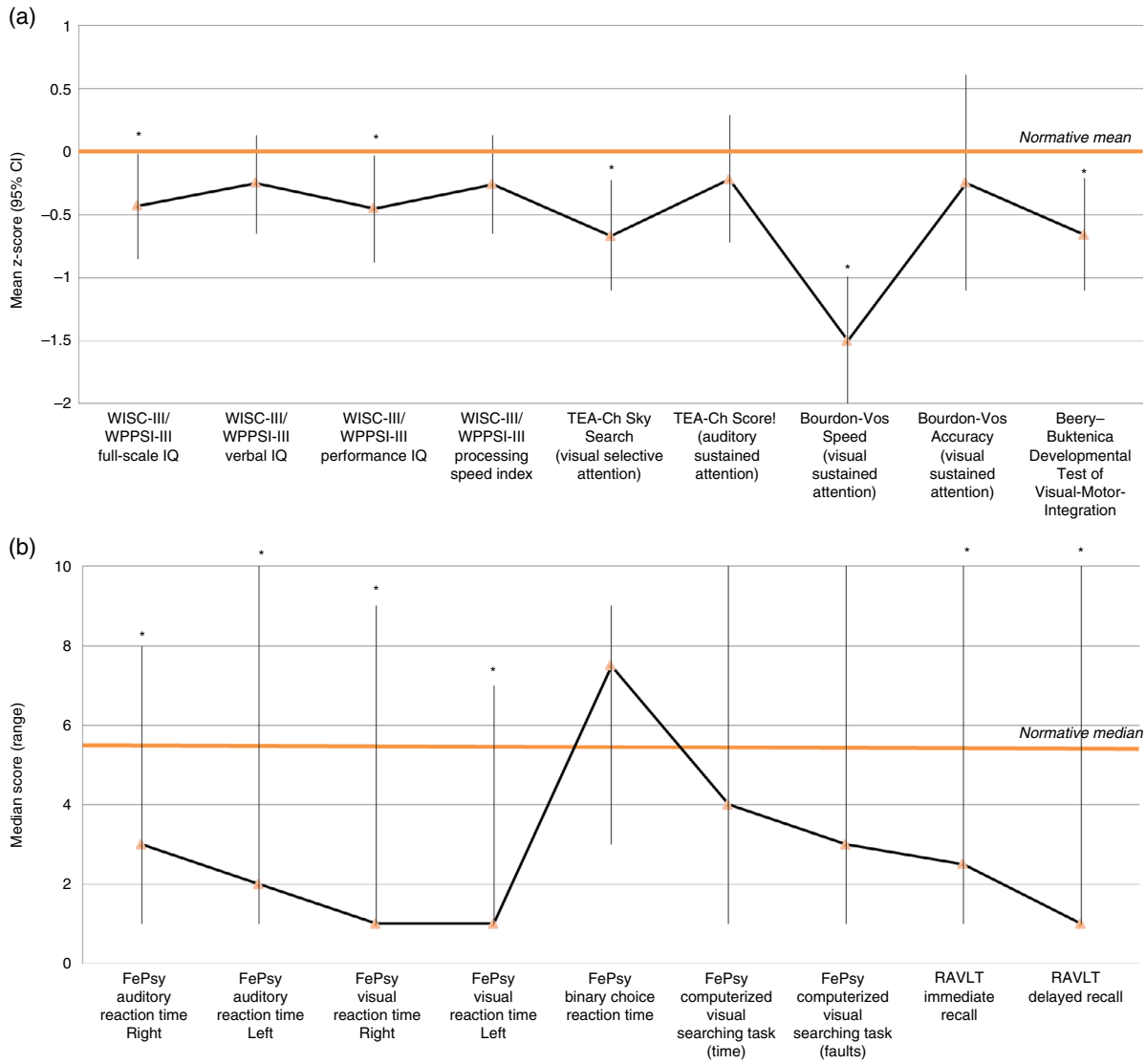

Figure 2: Neuropsychological profile of children with Panayiotopoulos syndrome. (a) z-scores and 95% confidence intervals (CIs). (b) Median scores and range. The asterisks represent statistically significant differences between mean or median scores compared to the normative median. WISC-III, Wechsler Intelligence Scale for Children, Third Edition; WPPS-III, Wechsler Preschool and Primary Scale of Intelligence, Third Edition; TEA-CH, Test of Everyday Attention for Children; RAVLT, Rey Auditory Verbal Learning Test. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 2: Educational achievement in the study cohort

Test	Subscore	*n*	Mean score (95% CI) indicates months behind/ahead	*p*
Speed reading	Words	11	−10.55 (−16.89 to −4.20)	**0.004**
	Sentences	10	−11.20 (−19.10 to −3.30)	**0.01**
Speed arithmetic	Arithmetic	9	−7.78 (−14.67 to −0.89)	**0.03**

The results from each test were compared with the normative mean. Bold type indicates statistical significance of $p \leq 0.05$.

visual searching task, and Wechsler Intelligence Scale for Children, Third Edition subtests of coding and symbol searching. Furthermore, our data suggest that cognitive dysfunctions are not limited to visually demanding tasks, since lower performance was also observed for auditory reaction times and verbal memory. However, slower auditory reaction times may contribute to decreased encoding of the verbal memory task. Germanò et al.[18] also found dysfunctions in the verbal and visual-spatial memory abilities in children with benign childhood epilepsy with occipital paroxysms. In a subset of patients, lower scores were also observed in the copy and recall tasks of the Rey–

Table 3: Behavioural problems in the study cohort

Test	Subscore	*n*	Median T score (range)	*p*
Child Behavior Checklist (by parent)	Internalizing behavioural problems	17	58.1 (52.06–64.06)	**0.01**
	Externalizing behavioural problems		53.2 (46.65–59.82)	0.31
	Total behavioural problems		58.1 (52.19–63.93)	**0.01**
Teacher's Report Form	Internalizing behavioural problems	9	55.8 (48.92–62.64)	0.09
	Externalizing behavioural problems		58.1 (49.94–66.29)	0.05
	Total behavioural problems		57.4 (49.75–65.14)	0.06

The results from each test were compared with the normative mean. Bold type indicates statistical significance of $p \leq 0.05$.

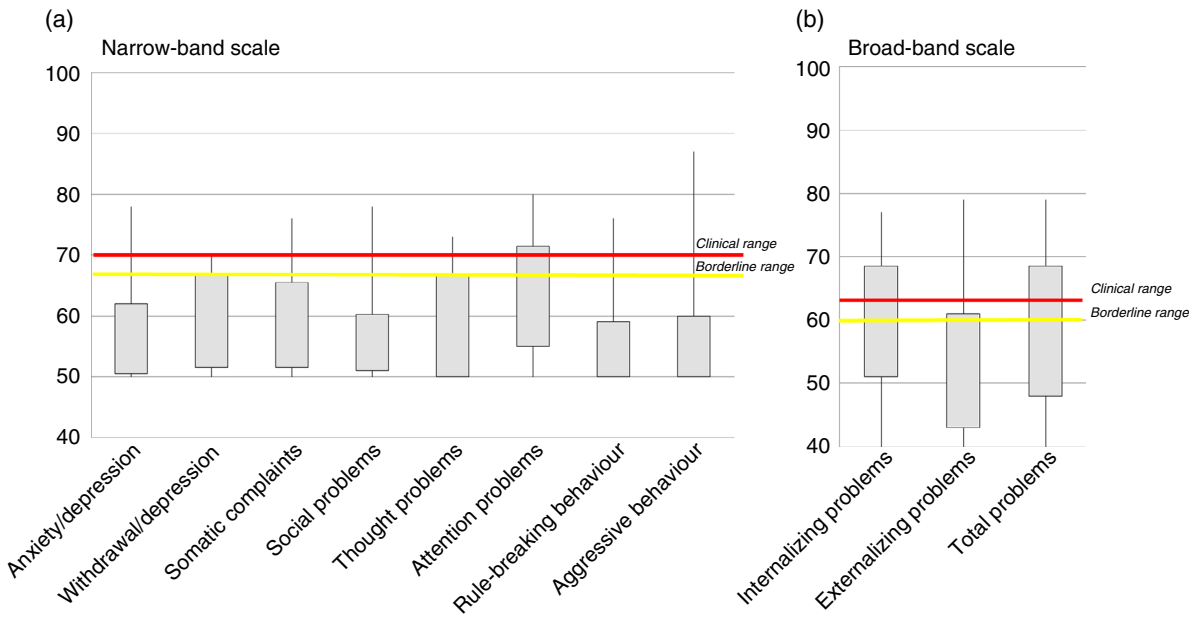

Figure 3: Behavioural profile of children with Panayiotopoulos syndrome based on the Child Behavior Checklist completed by parents. The quartile distribution of T scores is depicted in the boxplots. (a) A narrow-band T score between 67 and 70 is considered borderline; scores above 70 are considered as clinical scores. (b) A broad-band T score between 60 and 63 is considered borderline; scores above 63 are considered as clinical scores. [Colour figure can be viewed at wileyonlinelibrary.com]

Osterrieth Complex Figure Test (n=9) and the Beery–Buktenica motor coordination task (n=9), which may suggest dysfunctions in visual perception, memory, and/or motor programming (Appendix S2). More sensitive measures are needed to draw definitive conclusions on the specific brain areas or networks mediating cognitive deficits in individuals with Panayiotopoulos syndrome.

A study in six children with Panayiotopoulos syndrome suggested disruption of prefrontal growth in those children with status epilepticus, which was also reflected in cognitive and behavioural impairments.[13] Indeed, the relatively long duration of seizures in this population, as often seen in Panayiotopoulos syndrome, may have an impact on neurodevelopment, neurocognitive performance, and behaviour.

Furthermore, our study found a high incidence of reported internalizing behavioural problems in children with Panayiotopoulos syndrome. In particular, withdrawal/depression, thought problems, attention problems, and somatic complaints were reported more often. A meta-analysis by Rodenburg et al.[26] on behavioural problems in children with epilepsy also found more internalizing behavioural problems than in the general population. They concluded that attention, thought, and social problems were relatively specific to epilepsy in children in addition to the more general behavioural problems associated with chronic disease.

The neurocognitive and behavioural impairments associated with Panayiotopoulos syndrome question the benign nature of this syndrome, as has been questioned in other 'benign' epilepsy syndromes, such as absence epilepsy and benign epilepsy with centrotemporal spikes.[16,27] Nevertheless, an effect of AED treatment on cognitive performance cannot be entirely excluded based on this study. Children with Panayiotopoulos syndrome should be assessed for cognitive deficits, educational underachievement, and behavioural problems to ensure timely intervention. Ideally, this should be managed in an interdisciplinary fashion. If necessary, educational and emotional support programmes should be offered.

This study was performed in a tertiary epilepsy centre. Children with Panayiotopoulos syndrome were closely

monitored regarding the evolution of clinical, cognitive, and EEG aspects. Limitations include a relatively small sample size, the varying time points of the cognitive assessments, and the total follow-up time. From a clinical perspective, patients presented typically for Panayiotopoulos syndrome and did not seem to have a worse clinical prognosis. Total seizure frequency was low and seizure freedom with monotherapy was attained in the large majority. Use of AEDs in most of this population may have had a bearing on the results, although AED use did not correlate with cognitive performance in this study. Specifically, valproate (n=3) may have had an impact on attention in some based on a randomized controlled trial in childhood absence epilepsy,[28] but overall it does not seem to impair cognition.[29,30] Levetiracetam (n=4) does not seem to impair cognition, whereas there is no consensus as to what extent carbamazepine (n=5) or clobazam (n=2) impact cognitive performance.[29–31] Topiramate (n=1) has been associated with cognitive impairments in attention, memory, and language function.[29,30]

Data derived from a single (tertiary) centre may be biased due to possible referral of more severely affected children. The multitude of cognitive deficits and behavioural problems in this population were larger than could be expected by chance alone. Cautious interpretation of the results is necessary until replicated in future large prospective cohort studies.

CONCLUSION

Children with Panayiotopoulos syndrome demonstrated diffuse cognitive dysfunction in full-scale IQ, performance IQ, attention, visual-motor integration, and verbal memory. Moreover, a high incidence of internalizing behavioural problems were present. These findings strongly suggest neuropsychological and behavioural comorbidity in Panayiotopoulos syndrome.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table S1: Description of neurocognitive, educational achievement, and behavioural tests.

Table S2: Patient characteristics.

Appendix S1: References associated with the neuropsychological tests used in the study.

Appendix S2: Subtests of the Wechsler Intelligence Scale for Children and neurocognitive tests performed in a small subset of patients.

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